

Pharmacologic stress testing for coronary disease diagnosis: A meta-analysis

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Background Although noninvasive pharmacologic stress tests are widely used, their relative performance is not clear. We compared the performance of pharmacologic stress tests combined with echocardiography or nuclear imaging for the diagnosis of coronary disease.

Methods We performed a regression meta-analysis of published data. We included studies published between January 1975 and June 1999 in which subjects underwent echocardiographic or single-photon emission computed tomography (SPECT) stress testing with adenosine, dipyridamole, or dobutamine for diagnosis of coronary artery disease. All subjects also underwent coronary angiography. Two independent reviewers abstracted population characteristics, technical factors, methodologic factors, and results and calculated test sensitivity and specificity.

Results Eighty-two studies met the inclusion criteria. The sensitivity of dipyridamole SPECT imaging, 89% (95% CI, 84%-93%), was higher than that of dipyridamole echocardiography, but the specificity of dipyridamole SPECT imaging, 65% (95% CI, 54%-74%), was lower than that of dipyridamole echocardiography. Dipyridamole and adenosine tests had similar sensitivities and specificities. The sensitivity of dobutamine echocardiography, 80% (95% CI, 77%-83%) was similar to that of dobutamine SPECT imaging, but dobutamine echocardiography had a higher specificity, 84% (95% CI, 80%-86%) than dobutamine SPECT imaging did.

Conclusions The findings of our study can be used to guide the selection of the optimal pharmacologic stress test for each patient. Maximum sensitivity can be attained by use of a vasodilator combined with SPECT imaging. Maximum specificity can be attained by use of a vasodilator with echocardiography. The highest combination of sensitivity and specificity can be attained with dobutamine echocardiography. (*Am Heart J* 2001;142:934-44.)

Several types of noninvasive stress tests are available for the diagnosis of coronary artery disease (CAD). These tests combine either exercise or pharmacologic stress with an imaging method such as nuclear perfusion or echocardiography. The pharmacologic agent can be an inotrope such as dobutamine or a vasodilator such as adenosine or dipyridamole. There are numerous reports of the diagnostic characteristics of these stress tests, but study results vary widely. This inconsistency has been partially resolved by recent systematic meta-analyses on exercise testing, in all patients¹ and in women.²

A systematic review has not been done for all pharmacologic stress tests. Many patients are unable to undergo maximal exercise stress testing because of physical impairments or deconditioning. In these patients, pharmacologic agents replace exercise. Although reviews of pharmacologic stress testing have been conducted,³ they have not examined nuclear perfusion studies nor have they incorporated current methodologic recommendations for meta-analyses of diagnostic testing.⁴⁻⁷

Therefore we undertook a systematic meta-analysis of pharmacologic stress testing using summary receiver-operator characteristic curve (SROC) analysis. The SROC analysis allows for the summary of the sensitivity and specificity results from several studies into a single ROC curve, facilitating comparisons between tests. Sensitivity and specificity may vary between studies because of differences in the threshold for a positive test or differences in the population tested.⁶ We compare the accuracy of the most commonly used pharmacologic stress tests for diagnosis of CAD: vasodilator (adenosine or dipyridamole) or inotropic agent (dobutamine) combined with single-photon emission computed tomography (SPECT) imaging or echocardiography.

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Methods

Search for published data

We reviewed articles that studied noninvasive tests for CAD diagnosis using the inotropic agent dobutamine or the vasodilating agents dipyridamole or adenosine. We searched MEDLINE for English language studies with human subjects for each of these stressors using the search strategy "coronary disease/diagnosis AND (pharmacologic stress)." The searches covered a time period of January 1975 to June 1999. We also reviewed the reference lists of review articles and eligible studies and consulted with experts to complete the data search.

Selection criteria

Entry criteria for studies were (1) all subjects underwent at least one pharmacologic stress test with either echocardiography or SPECT and coronary angiography, the reference standard for CAD diagnosis, and (2) data presentation in a manner that allowed calculation of the sensitivity and specificity of the tests. Excluded were (1) studies for post-myocardial infarction risk stratification, post-coronary artery bypass grafting or postangioplasty evaluation, or cardiac transplant evaluation, (2) studies combining exercise with pharmacologic stress (except in the case of hand grip exercise), (3) studies using oral pharmacologic agents, (4) studies in special subgroups such as patients with significant chronic renal insufficiency or aortic stenosis, and (5) studies that likely presented duplicate data. These studies included data from previous publications, usually presented in a different analysis. In these cases, only the study with the largest number of subjects was selected for inclusion.

Data collection

Two reviewers independently abstracted the eligible articles. Disagreements between reviewers were resolved by conference. Information abstracted from each report included population characteristics, technical factors, methodologic factors, and results. For each study we recorded publication year, type of test, total number of participants, number of male and female participants, mean age, type of pharmacologic stress, type of imaging modality, percentage of patients with myocardial infarction (MI), angiographic definition of coronary disease, and percentage of participants with CAD by angiography (Table 1). For studies of nuclear perfusion, we recorded whether thallium 201 or technetium 99m sestamibi was the nuclear isotope and whether all defects or only reversible defects were considered "positive" tests.

For subgroup analysis, we abstracted data on test performance by sex if the data were available. We compared the performance of thallium versus sestamibi isotope. If available, we also recorded test performance in multivessel disease. The literature varied on how detection of multivessel disease was defined. In some studies, detection of multivessel disease was defined as any positive test. In others, the sensitivity and specificity for multivessel disease was determined by abnormalities in 2 or more vascular territories. We calculated test performance for both definitions and present them separately.

We rated methodologic quality on the basis of 3 criteria: adequate description of the study group, potential for verification bias, and potential for diagnostic and test review bias.⁵ An

adequate description entailed clearly defined participant selection criteria and characteristics. Verification bias was avoided if the results of the pharmacologic stress test did not influence the decision to perform angiography. Diagnostic and test review biases were absent if both the noninvasive test and angiography were read blindly. We classified studies "high quality" if they met all 3 methodologic criteria, "medium quality" if they met 2 criteria, and "low quality" if they met 1 or none of the criteria (Table 1).

Statistical analysis

For each study we calculated sensitivity and specificity. Using the sample size for the patients with and without CAD, we calculated weighted average sensitivities and specificities and constructed SROC curves for each pharmacologic stress test. Use of an ROC curve allows simultaneous evaluation of sensitivity and specificity and facilitates test comparison. An ROC regression analysis also can determine the influence of covariates on test accuracy.⁶

For SROC regression analysis, we performed a weighted least-squares regression analysis using $D = \log(\text{sensitivity}) - \log(1 - \text{specificity})$ as the response variable with $S = \log(\text{sensitivity}) + \log(1 - \text{specificity})$ as one of the predictor variables.⁶ With use of a model that specifies $D = \alpha + \beta \cdot S$ defines an ROC curve by the intercept α and the slope β . Covariates may influence both the intercept or the slope. If a covariate, X , only influences the SROC intercept and not the slope (ie, is a main effect), then the ROC curves for different values of X will not cross; hence X is purely associated with differences in accuracy. We used weights for each observation that were proportional to the inverse of the variance of D . We also used SE estimates that are robust to misspecification of the variance (ie, corrected for possible overdispersion) according to the method of Huber.⁷

To determine whether certain study-specific covariates are correlated with test accuracy, we used SROC regression models that included the additional variables: publication year, age of subjects, methodologic quality (high, medium, low), absence of verification bias, definition of coronary disease (50% or 70% stenosis), coronary disease prevalence, percentage of subjects with history of myocardial infarction, and percentage of male subjects. For nuclear studies, we analyzed the effect of choice of isotope (thallium or sestamibi), and the definition of a positive test. We included the factors with a univariate $P < .20$ in a multivariate regression and then used backward elimination to remove variables that did not achieve a .05 level of significance. Subgroup analyses were carried out for results for men and women separately and multivessel disease, if there were more than 3 studies that presented data for each subgroup. All calculations were performed with S-PLUS software.⁹⁰

Results

Search for published data

Initial data searches yielded 605 titles for studies using dipyridamole, 474 titles for studies using dobutamine, and 297 titles for studies using adenosine, for a total of 1379 studies. By reviewing titles and abstracts, we excluded 1129 articles with no original data and

Table I. Characteristics of studies included in meta-analysis

Author	Year	Test(s) studied	No.	Women (%)	With CAD (%)	Mean age (y)	With prior MI (%)	CAD definition*	Verification†	Quality‡
Aksut et al ⁸	1995	AS	443	40	90	63	24	50%	No	Low
Allman et al ⁹	1992	AS	76	43	79	63	0	50%	No	Medium
Amanullah et al ¹⁰	1993	AE, AS	40	20	85	61	30	50%	Yes	High
Amanullah et al ¹¹	1997	AS	222	46	77	71	0	50%	No	Low
Anthopoulos et al ¹²	1997	AE, DE	128	39	76	73	30	50%	Yes	High
Anthopoulos et al ¹³	1996	AE, DE	120	40	74	75	40	50%	Yes	High
Beer et al ¹⁴	1989	PS	65	40	74	61	45	50%	No	Low
Beleslin et al ¹⁵	1999	DE, PE	168	18	76	51	50	50%	Yes	High
Burns et al ¹⁶	1991	PS	16	31	50	63	6	50%	No	Low
Cecil et al ¹⁷	1996	PS	211		53		0	50%	Yes	Medium
Cohen et al ¹⁸	1991	DE	70	0	73	62	27	70%	Yes	High
Cohen et al ¹⁹	1993	DE	52	2	71	63	25	70%	Yes	High
Dagianti et al ²⁰	1995	DE, PE	64	30	42	54	0	70%	Yes	High
Daoud et al ²¹	1995	DE	76	42	86	60	37	50%	No	Low
DePuey et al ²²	1990	PS	76	37	67	63		50%	No	Medium
DiBello et al ²³	1996	DE, DS	45	27	84	53	0	50%	Yes	High
Dionisopoulos et al ²⁴	1997	DE	288	35	73	61	0	50%	No	Medium
Djordjevic-Dikic et al ²⁵	1996	AE	58	12	69	50	43	50%	Yes	High
Ebersole et al ²⁶	1993	AS	11	73	27	62		50%	Yes	High
Elhendy et al ²⁷	1998	DS	70	100	64	58	34	50%	No	Low
Elhendy et al ²⁸	1997	DE	306	31	76	58	70	50%	No	Low
Epstein et al ²⁹	1992	DE	61	30	87	59		50%	No	Low
Ferrara et al ³⁰	1991	PE	130	38	83	61	5	70%	Yes	Medium
Go et al ³¹	1990	PS	202		75		47	50%	No	Low
Grover-McKay et al ³²	1994	PS	18	0	61	61		50%	No	Medium
Gunalp et al ³³	1993	DE, DS	27	15	67	47	0	50%	No	Low
Hayashi et al ³⁴	1991	PS	31	32	74	57	39	50%	Yes	High
Hennessy et al ³⁵	1997	DE	219	36	78	69	24	50%	Yes	High
Ho et al ³⁶	1997	DE	206		78	58	42.5	50%	Yes	Medium
Ho et al ³⁷	1995	DE, PS	54	15	80	58	41	50%	No	Medium
Hoffman et al ³⁸	1993	DE	64	23	75	57	0	70%	Yes	High
Huang et al ³⁹	1998	DS	110	26	59	61	0	50%	No	Low
Huang et al ⁴⁰	1997	DS	93	23	72	61	39	50%	Yes	Medium
Huikuri et al ⁴¹	1989	PS	33	64	33	59	0	50%	Yes	High
John et al ⁴²	1992	PS	31	0	94	56		50%	Yes	High
LaManna et al ⁴³	1990	AS	15		100	58		50%	No	Low
Lattanzi et al ⁴⁴	1992	PE	28	11	75	54	32	70%	Yes	High
Lewis et al ⁴⁵	1999	DE	92	100	27	57		50%	No	Medium
Mandysova et al ⁴⁶	1991	PE	53	9	75	55	66	70%	Yes	Medium
Marangelli et al ⁴⁷	1994	PE	82	16	58	58	0	70%	Yes	Medium
Marcovitz and Armstrong ⁴⁸	1992	DE	141	40	77	60		50%	No	Low
Marwick et al ⁴⁹	1993	DE, DS	217	28	65	56	0	50%	Yes	Medium
Marwick et al ⁵⁰	1993	AE, AS, DE, DS	97	29	61	56	0	50%	Yes	Medium
Marwick et al ⁵¹	1994	DE, DS	86	30	65	59	0	50%	Yes	High
Mazeika et al ⁵²	1991	PE	55	25	73	55		70%	No	Medium
Mazeika et al ⁵³	1992	DE	50	12	72	54	26	70%	Yes	High
McNeill et al ⁵⁴	1992	DE	80	26	59	60	35	50%	Yes	Medium
Mendelson et al ⁵⁵	1992	PS	79	27	62	60	70	70%	No	Medium
Miller et al ⁵⁶	1997	PS	244	1	84	62.8	35	50%	No	Low
Mohiuddin et al ⁵⁷	1996	AS	202	41	79	58	22	50%	No	Medium
Nagel et al ⁵⁸	1999	DE	186	33	63	60		50%	Yes	High
Nishimura et al ⁵⁹	1991	AS	101	41	69	64	44	50%	No	Low
Ogilby et al ⁶⁰	1998	PS	26	27	77	57	38	50%	No	Medium
Ostojic et al ⁶¹	1994	DE, PE	150	17	87	51	50	50%	No	Medium

AS, Adenosine SPECT; AE, adenosine echocardiography; DE, dobutamine echocardiography; PS, dipyridamole SPECT; PE, dipyridamole echocardiography; DS, dobutamine SPECT.

*Luminal narrowing of ≥ 1 coronary artery on angiography required for diagnosis of CAD.

†Absence of verification bias.

‡Quality score; see Methods.

Table I. Continued. Characteristics of studies included in meta-analysis

Author	Year	Test(s) studied	No.	Women (%)	With CAD (%)	Mean age (y)	With prior MI (%)	CAD definition*	Verification†	Quality‡
Pennell et al ⁶²	1990	PS	40	18	98	54	58	50%	No	Medium
Pennell et al ⁶³	1993	PS	42	21	98	54	33	50%	No	Low
Pennell et al ⁶⁴	1991	DS	50	16	80	54	30	50%	Yes	High
Picano et al ⁶⁵	1994	PE	31	39	58	53	0	50%	No	Medium
Picano et al ⁶⁶	1987	PE	55	16	62	52	11	70%	No	Medium
Pingitore et al ⁶⁷	1996	DE, PE	110		84			50%	No	Low
Previtali et al ⁶⁸	1993	DE, PE	80	23	71	53	19	50%	No	Medium
Sahin et al ⁶⁹	1994	DE	65	29	65	58		50%	Yes	High
Salustri et al ⁷⁰	1992	DE, PE	46	30	61	58	33	50%	Yes	Medium
San Roman et al ⁷¹	1998	DE, DS, PE	102	51	65	64	0	50%	Yes	High
San Roman et al ⁷²	1996	DE, PE	102	44	62	62	0	50%	Yes	Medium
Santoro et al ⁷³	1998	DE, DS, PE, PS	60		55		0	70%	Yes	Medium
Schillaci et al ⁷⁴	1997	PE, PS	40	38	55	55	0	70%	No	Low
Segar et al ⁷⁵	1992	DE	85	39	75	59		50%	No	Medium
Senior et al ⁷⁶	1998	DE	121	23	49	62	29	70%	Yes	High
Senior et al ⁷⁷	1994	DE, DS	61	28	72	63	21	50%	No	Medium
Severi et al ⁷⁸	1994	PE	429	28	57	55	0	70%	Yes	High
Simonetti et al ⁷⁹	1991	PE	51	22	76	52		70%	Yes	Medium
Slavich et al ⁸⁰	1996	DE, DS	46	100	48	59	0	50%	No	Medium
Sochowski et al ⁸¹	1995	DE, PE	46	33	54	58	0	70%	Yes	High
Soman et al ⁸²	1997	PS	27	33	78	58	18	50%	Yes	High
Takeuchi et al ⁸³	1993	DE	120	26	62	63	52	50%	Yes	Medium
Takeuchi et al ⁸⁴	1996	DE, PS	70	100	29	65	0	50%	Yes	High
Tartagni et al ⁸⁵	1991	PS	30	13	87	59	57	70%	No	Low
Vitarelli et al ⁸⁶	1997	DE	59	36	81	52		70%	No	Low
Warner et al ⁸⁷	1993	DE, DS	16	56	94	61	56	50%	Yes	High
Watanabe et al ⁸⁸	1997	PS	70	33	59	63	23	50%	Yes	High
Zoghbi et al ⁸⁹	1991	AE	73	15	82	59	52	50%	No	Medium

studies that did not include both angiography and stress testing. We reviewed the text of the remaining articles and further excluded articles using the above criteria, including 29 studies with likely duplicate data, although the objectives of the studies differed.⁹¹⁻¹¹⁷ Thus we identified 82 studies that met all the inclusion criteria.⁸⁻⁸⁹ Some studies included data on more than one test. Overall, 6 studies presented data on adenosine echocardiography, 9 on adenosine SPECT imaging, 40 on dobutamine echocardiography, 14 on dobutamine SPECT imaging, 20 on dipyridamole echocardiography, and 21 on dipyridamole SPECT imaging (Table II).

SPECT imaging versus echocardiography

There were 3737 patients in 44 studies using SPECT imaging and 6448 patients in 66 studies using echocardiography. Vasodilator SPECT imaging offered higher sensitivity but lower specificity than did vasodilator echocardiography. Dobutamine SPECT imaging offered similar sensitivity but lower specificity than did dobutamine echocardiography (Table II).

SPECT imaging

Of the 3 pharmacologic stressors, dipyridamole was the most commonly combined with SPECT imaging.

SPECT studies used either thallium or sestamibi as the nuclear isotope. There were 2112 patients in 23 studies with thallium and 1625 patients in 21 studies with sestamibi. The 2 isotopes had similar sensitivities and specificities for all pharmacologic stressors (results not shown). The majority of studies defined a positive test as any imaging abnormality; only 2 studies defined a positive test as a “reversible” defect.

Of the 30 studies of vasodilator SPECT imaging, most used thallium as the imaging agent. The sensitivity and specificity of dipyridamole SPECT imaging were not significantly different from those of adenosine SPECT imaging (Table II). In contrast, most of the 14 studies of dobutamine SPECT studies used sestamibi as the imaging agent. Compared with studies of vasodilator SPECT, dobutamine SPECT studies had a lower sensitivity but similar specificity (Table II).

Echocardiography

Of the 3 pharmacologic stressors, dobutamine was the most commonly combined with echocardiography. Dobutamine echocardiography had a higher sensitivity but a lower specificity than did dipyridamole or adenosine echocardiography. The 20 studies of dipyridamole echocardiography had a sensitivity and specificity that

Table II. Weighted mean sensitivities, specificities of pharmacologic studies

Pharmacologic test	Studies	Subjects	Mean age (y)	CAD (%)	MI (%)	Men (%)	Sensitivity (% [95% CI])	Specificity (% [95% CI])
Adenosine echocardiography	6	516	65	73	31	71	72 (62-79)	91 (88-93)
Adenosine SPECT	9	1,207	63	80	17	59	90 (89-92)	75 (70-79)
Dipyridamole echocardiography	20	1,835	56	67	15	72	70 (66-74)	93 (90-95)
Dipyridamole SPECT	21	1,464	60	71	31	77	89 (84-93)	65 (54-74)
Dobutamine echocardiography*	40	4,097	59	70	26	66	80 (77-83)	84 (80-86)
Dobutamine SPECT	14	1,066	58	66	9	63	82 (77-87)	75 (70-79)
Total	120†	10,817						

*One dobutamine echocardiographic study not included here because only multivessel disease was examined.

†Total number of tests exceeds the number of studies reviewed because some studies examined more than one pharmacologic test.

Table III. Sex-specific weighted mean sensitivities and specificities

Pharmacologic test	Studies	Subjects	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
Men				
Dipyridamole echocardiography	4	558	76 (71-80)	88 (81-93)
Dobutamine echocardiography	5	522	78 (74-82)	89 (82-94)
Women				
Dobutamine echocardiography	5	365	76 (69-82)	86 (80-91)

were not significantly different from those of adenosine echocardiography (Table II).

Sex-specific results

Few studies presented sex-specific data (Table III). There were only enough studies for subgroup analysis for dobutamine echocardiography and dipyridamole echocardiography for men and dobutamine echocardiography for women. There were no statistically significant differences between the sex-specific results and the results for all patients because many of the studies included women but did not report results separately. The confidence intervals are broad, reflecting the paucity of studies and subjects that presented sex-specific data (Table III).

Multivessel disease

We examined the issue of multivessel disease in 2 ways. First, we looked only at whether the noninvasive test showed any imaging abnormality in the presence of multivessel disease on cardiac catheterization. In this instance we did not take into account the degree of abnormality or the number of vascular territories identified on the noninvasive imaging studies. Thus an echocardiographic study showing only a lateral wall motion abnormality in a subject with triple-vessel disease would count as a true-positive test. By this definition the sensitivity of the finding of any imaging abnormality can be calculated in patients with multivessel disease. Many studies used this definition (Table IV).

The second definition of multivessel disease required

that noninvasive imaging studies show abnormalities in ≥ 2 vascular territories to be considered positive for the presence of multivessel disease. For example, an echocardiographic study showing only a lateral wall motion abnormality in a subject with triple-vessel disease would count as a negative test. At least 2 vascular territories would have to be abnormal on the echocardiogram for the test to be positive. Exact matching of the abnormal imaging areas to the diseased vessels was not required. This allows for the calculation of the sensitivity and specificity for the finding of imaging abnormalities in multiple vascular territories. Fewer studies presented data in this format (Table IV). As expected, the sensitivity calculated by use of this definition for the detection of multivessel disease is significantly lower than the less-exact first definition. However, the specificity of finding imaging abnormalities in >2 vascular territories compares favorably with the specificities for the detection of CAD in general. In particular, dipyridamole and dobutamine nuclear imaging studies have higher specificities for multivessel CAD detection than they do for general CAD detection. Thus the presence of multiple imaging abnormalities seems to be a specific but not a sensitive marker of multivessel disease.

SROC analysis

The shape of the ROC curve for dobutamine is different from the ROC curve for dipyridamole, with dobutamine having a sharper increase in sensitivity for a given increase in the false-positive rate. Figure 1 shows the

Table IV. Weighted mean sensitivities and specificities for the detection of multivessel disease

Pharmacologic test	Studies	Subjects	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
Definition of positive = any imaging abnormality				
Adenosine echocardiography	6	522	75 (69-81)	Not calculable
Adenosine SPECT	4	843	92 (89-95)	Not calculable
Dipyridamole echocardiography	11	1139	82 (78-85)	Not calculable
Dipyridamole SPECT	10	671	91 (87-94)	Not calculable
Dobutamine echocardiography	30	3080	86 (83-88)	Not calculable
Dobutamine SPECT	9	834	84 (80-88)	Not calculable
Definition of positive = ≥ 2 vascular areas with abnormalities				
Dipyridamole SPECT	4	182	59 (48-69)	85 (76-92)
Dobutamine echocardiography	7	921	53 (47-59)	82 (79-85)
Dobutamine SPECT	5	505	44 (37-52)	88 (84-92)

weighted average (true-positive, false-positive) pairs for the combinations of stressor and imaging method. The SROC regression analysis suggests that the observed differences in sensitivity and specificity are consistent with the classic tradeoff between sensitivity and specificity that is observed for a continuous diagnostic measurement when operating with different thresholds for declaring a positive test.

In the analysis of covariates, the variables of age, percent with MI history, study quality score, thallium and sestamibi, and percent men all have significance levels $\geq .20$, suggesting that these factors do not influence accuracy. Variables included in a backward elimination model were publication year, verification bias, 50% stenosis definition, and proportion of patients with CAD. Of these, only 50% stenosis for disease definition ($\beta -0.648, P = .003$) and percent of subjects with CAD ($\beta 1.691, P = .014$) showed significance.

Because of concerns regarding verification bias, we compared sensitivities and specificities between studies that did not have verification bias and studies that did have verification bias. There was no significant difference in the results between studies that controlled for verification bias and studies that did not, for any test (results not shown).

Discussion

In this meta-analysis, SPECT studies offered greater sensitivity and echocardiographic studies offered greater specificity. Clinicians can choose the appropriate test for their patients depending on the suspicion of coronary disease.

As expected, tests that use adenosine and dipyridamole yield interchangeable results. Both agents are coronary vasodilators; dipyridamole works by increasing intra-arterial levels of adenosine. Both agents cause nondiseased coronary arteries to undergo greater

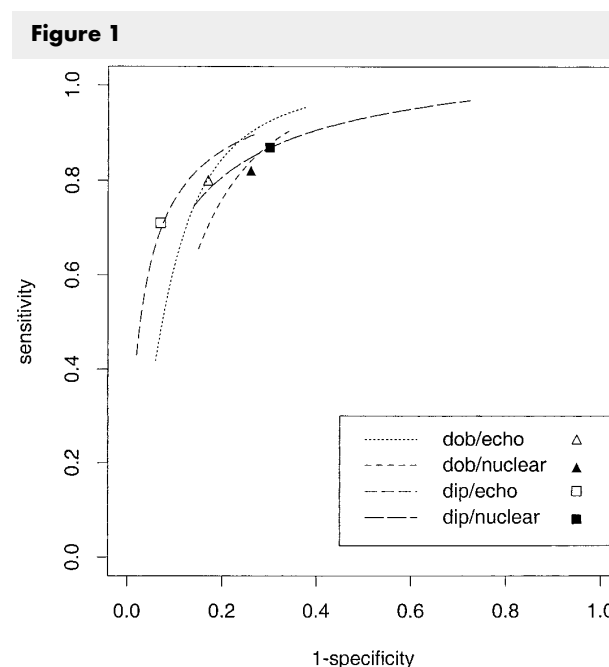


Figure 1
SROC curve. The summary curves are only presented for a limited range of sensitivities and specificities to not exceed the observed range of true-positive and false-positive rates reported by studies for a given diagnostic test. Adenosine and dipyridamole (*dip*) are virtually identical, so only dipyridamole is shown. *dob*, Dobutamine; *echo*, echocardiography.

vasodilatation, leading to a “steal” of blood flow away from myocardium perfused by diseased coronary arteries. The selection of either agent is generally based on considerations such as side effects, cost, availability, and familiarity with the agent.

When echocardiographic and SPECT vasodilator studies are compared, we see that adenosine and dipyridamole SPECT studies offer the highest sensitivities,

90% and 89%, respectively. Adenosine and dipyridamole echocardiographic studies offer the highest specificities, 91% and 93%, respectively. Thus the choice of the imaging modality for vasodilator studies seems to involve a tradeoff of higher sensitivity or specificity.

The results with dobutamine are significantly different than the results with the vasodilators. Dobutamine is an inotropic agent; instead of primarily affecting myocardial blood supply, dobutamine primarily increases myocardial demand by increasing heart rate and contractility. Thus, as a stressor, it is more comparable to exercise. Not surprisingly, dobutamine echocardiography and nuclear imaging results are comparable with the results from a previous study of exercise echocardiography and SPECT imaging.¹ The sensitivities of dobutamine echocardiography (80%) and dobutamine SPECT imaging (82%) are similar, as are the sensitivities of exercise echocardiography (85%) and exercise SPECT imaging (87%). Similarly, the specificity of dobutamine echocardiography (84%) is higher than that of dobutamine SPECT imaging (75%), and the specificity of exercise echocardiography (77%) is higher than that exercise SPECT imaging (64%). This suggests that echocardiography may be a better myocardial imaging modality for both dobutamine and exercise studies. Exercise studies offer a slightly higher sensitivity and a lower specificity than dobutamine studies. Of course, only exercise studies offer functional data.

The results in the sex subanalysis are limited by the fact that few studies presented sex-specific data. However, dobutamine echocardiography had a similar sensitivity and specificity in women and men, a finding that had also been confirmed in exercise echocardiographic studies.²

The finding of imaging abnormalities in >2 vascular territories appears to be a specific although not sensitive finding for the detection of multivessel disease. In clinical practice, the degree of abnormality on the imaging study is often as important as whether a study is "positive" or "negative." Our data show that extensive imaging abnormality, if present, is a reliable sign of more extensive underlying disease, especially in nuclear imaging studies.

Several limitations of our study must be considered. First, like most meta-analyses, our study is subject to publication bias. Only published studies were examined, mostly from academic centers expert in the techniques. A previous study has demonstrated that high-volume echocardiographers had higher accuracy than "beginners" did.¹¹⁸ Also, studies with poor results are less likely to be accepted for publication. Therefore our results may be better than those achieved in actual practice. Second, as in all meta-analyses of diagnostic testing, verification bias is an important limitation of our study, given that about half the studies included in

our meta-analysis did not control for this. Verification bias occurs when the result of the test influences which patients will receive the verification test. This can have dramatic results on the sensitivity and specificity of a test.¹¹⁹ We are unable to correct for this bias because the original studies do not provide information on the entire population tested. However, in our covariate analyses, we failed to find a significant difference between studies that did and did not control for verification bias. Also, this bias is likely to similarly occur in studies of adenosine, dipyridamole, and dobutamine, allowing comparisons between types of testing. Studies varied widely in publication year, so it is possible that the accuracy of older tests might falsely appear to be lower, but interestingly, there was no increase in accuracy in more recent studies in the SROC analysis.

The findings of our study can be used to guide the selection of the optimal pharmacologic stress test for each patient. Maximum specificity can be attained by use of a vasodilator with echocardiography. Maximum sensitivity can be attained by use of a vasodilator combined with nuclear imaging. Dobutamine echocardiography offers a good compromise between sensitivity and specificity. The clinician can customize the test selection to the clinical situation.

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